Remarks

No new matter has been entered by this amendment. Applicants believe that it is proper for the present amendment to be entered since it places the claims in better form for appeal, reduces the number of issues on appeal, does not raise any new issues, and does not require further consideration or search.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 7-12 and 15-25 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled for (1) *in vivo* methods of targeted recombination in which a triplex forming oligonucleotide (TFO) is utilized which has a Kd of **more than** $2x10^{-7}$ and (2) *in vivo* methods of targeted recombination that produces changes in the genome of an intact animal or human. Applicants respectfully traverse this rejection.

The Legal Standard for Enablement

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (See, e.g., *Amgen v. Hoechst Marion Roussell* 314 F.3d 1313 (Fed. Cir. 2003);*Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright* , 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)); See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such

experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir.1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation ' must not be unduly extensive.'*In re Atlas Powder Co., v. E.I. DuPont De Nemours & Co.* , 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir.1984).

As noted in *Ex parte Jackson*, the test is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired

embodiment of the invention claimed. See *Ex parte Jackson*, 217 USPQ 804, 807 (PTO Bd. App. 1982). There is no requirement for examples.

Claims 7-12 and 15-25 are enabled

(1) The examiner indicates on page 2 of the office action that the claims are not enabled for methods for *in vivo* targeted recombination or methods of targeted recombination in which a TFO is utilized which has a Kd of **more than** 2×10^{-7}. **The claims do not define methods of targeted recombination in which a TFO is utilized which has a Kd of more than** 2×10^{-7}. Claim 7 defines A method for targeted recombination of a nucleic acid molecule comprising the steps of: a) providing a single-stranded oligonucleotide having a sequence that forms a triple-stranded nucleic acid molecule by hybridizing with a target sequence in a double-stranded nucleic acid molecule with a Kd of **less than or equal to** 2×10^{-7}; and b) providing a donor nucleic acid such that recombination of the donor nucleic acid into the target sequence is induced by triple helix formation between the single-stranded oligonucleotide and the double-stranded nucleic acid molecule. The Examiner states of page 2 of the Office Action that claims wherein the TFO has a Kd of less than 2×10^{-7} are enabled. Therefore, the examiner's rejection is moot since the claims do not recite a Kd of "more than" 2×10^{-7} and claims 7-12 and 15-25 are enabled.

(2) The examiner also maintains that claims 7-12 and 15-25 are not enabled for *in vivo* methods of targeted recombination that produces changes in the genome of an intact animal or human.

The Claimed Invention

The Applicants have discovered that administration of a TFO in combination with a DNA fragment or "donor nucleic acid" promotes site-specific targeted recombination of the donor nucleic acid into the target region. The DNA fragment may be tethered to the TFO or not as described in the specification at least at page 7, lines 12-19. Claim 7 defines a method for targeted recombination of a nucleic acid molecule comprising the steps of: a) providing a single-stranded oligonucleotide having a sequence that forms a triple-stranded nucleic acid molecule by hybridizing with a target sequence in a double-stranded nucleic acid molecule with a Kd of less than or equal to 2×10^{-7}; and b) providing a donor nucleic acid such that recombination of the donor nucleic acid into the target sequence is induced by triple helix formation between the single-stranded oligonucleotide and the double-stranded nucleic acid molecule. Claim 15 defines the method of claim 7 to produce changes in the genome of an intact human or animal comprising the steps of: administering the single-stranded oligonucleotide into an intact human or animal having a sequence that forms a triple-stranded nucleic acid molecule with the target sequence located in the genome of the intact human or animal, wherein the oligonucleotide binds to the target sequence with a Kd of less than or equal to 2×10^{-7}, and mutates the target sequence.

An analysis of the Wands factors clearly demonstrates that claims 7-12 and 15-25 are enabled by the specification of the present application.

Methods for insertion of a homologous DNA sequence or DNA fragment *in vivo* were known to one of ordinary skill in the art and are described in the specification at least at page 3, lines 2-19. However, these methods are limited in their efficacy. Methods of targeting TFOs to

a specific site in the genome were known to one of ordinary skill in the art and are described in the specification at least at page 2, lines 1-5. It is understood by one of ordinary skill in the art that TFOs have at most two targets in the genome since there are only 2 copies of every chromosome. Single-stranded oligonucleotides having a sequence that forms a triple-stranded molecule by hybridizing with a target sequence in a double-stranded nucleic acid molecule are described in the specification at least at page 7 to page 11. Methods for targeted recombination of a target sequence using a single-stranded oligonucleotide as described in the specification at least at pages 7-11 and a donor nucleic acid such that the donor nucleic acid is recombined into the target sequence are described in the specification at least at page 9, lines 11-28 and page 14, lines 8-25. Methods of tethering or linking a donor nucleic acid to the single stranded oligunucleotide are described in the specification at least at page 17, lines 19-26. Methods of administration of the single-stranded oligonucleotide and donor nucleic acid *in vitro* and *in vivo* are described in the specification at least at page 11, line 17 to page 12, line 13 and at page 14, lines 8-19. The specification at least at page 11, lines 17-24 discloses that the oligonucleotides (i.e: the single-stranded oligonucleotide and donor nucleic acid) are dissolved in a physiologically-acceptable carrier and are injected into a human or animal. As discussed in the Declaration filed by Dr. Peter Glazer in the parent application U.S. Serial No. 09/411,291 now U.S. Patent No. 6,303,376, and described in the specification at least at page 11, lines 22-24, nucleic acid molecules are taken up by cells and tissues in animals such as mice without special delivery methods, vehicles or solutions. The *in vivo* distribution of oligonucleotides had been studied with a variety of modified oligonucleotides in mice (Zendegui, et al., *Nucleic Acids*

Research 20:307-314 (1992) and Agrawal, et al., *Proc. Natl. Acad. Sci.* USA 88, 7595 (1991), copies of which are enclosed). **These studies established that DNA molecules can be administered by i.p. or intravenous injections and gain access to tissues (outside the central nervous system) and to cell nuclei.** As expected from these studies, chromosomal DNA throughout the somatic tissues of an animal can be targeted by nucleic acids, which is also demonstrated by the applicant and described in the specification at least at examples 6 and 7, pages 31-35.

The Wands Factors

(i) quantity of experimentation, the amount of direction or guidance presented in the specification, and presence of working example

Since *in vivo* distribution of nucleic acids is achieved by injection of nucleic acids, all that is required to practice the method as defined by the claims is injection of a TFO linked or unlinked to a donor nucleic acid. Therefore, it is clear that the quantity of experimentation required to practice the claimed method is minimal. It is also clear from the amount of guidance provided in the specification as discussed above that the amount of experimentation required to practice the claimed method is not undue. Therefore, given the guidance provided in the specification, it would not require undue experimentation to practice the method of targeted recombination as defined by claims 7-12 and 15-25.

(ii) the state of the prior art, relative skill of those in the art, and the predictability of the art

Given the state of the art as discussed above the relative skill of those in the art was high and there was predictability in the art. Methods for insertion of a homologous DNA sequence or DNA fragment *in vivo* and methods of targeting TFOs to a specific site in the genome were known to one of ordinary skill. The specification at least at pages 21-22 and Table 1discloses that TFOs result in site-directed mutagenesis *in vitro*. Given the knowledge of one of ordinary skill in the art that for *in vivo* distribution of nucleic acids all that is required is injection of the nucleic acids, one of ordinary skill in the art would expect that a TFO injected into an animal would result in site-directed mutagenesis as predicted by the *in vitro* data. Indeed this is exactly what applicants demonstrate in Examples 6 and 7 that the TFO resulted in site-directed mutagenesis *in vivo* as predicted from the *in vitro* data. One of ordinary skill in the art would expect that injection of nucleic acid molecules as defined by the claims into an animal results in distribution of the nucleic acid molecules to tissues and cell nuclei and results in targeted recombination of a donor nucleic acid into a target DNA sequence. Therefore, it would not require undue experimentation to practice the method for targeted recombination *in vivo* as defined by claims 7-12 and 15-25.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 15-24 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for being unclear as to the relationship between the single stranded oligonucleotide and the donor nucleic acid in claim 7 and claims 15-24. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The test for definiteness under 35 U.S.C. § 112, second paragraph, is whether "**those skilled in the art would understand what is claimed when the claim is read in light of the specification.**" *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). It cannot be doubted that the claim itself must not be divorced in a vacuum from the specifications and descriptions accompanying it (See, e.g., *Schering Corp v. Gilbert*, 153 F.2d 428, 432 (2d Cir. 1946). The M.P.E.P. explains that the examiner's focus during examination of claims for compliance with the definiteness requirement "is whether the claim meets the threshold requirements of clarity and precision, *not whether more suitable language or modes of expression are available.*" (M.P.E.P. 2173.02, emphasis added) The M.P.E.P. further explains that "[s]ome latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire." (*Id.*)

Claim 15 has been amended to delete "further" to clearly define that there are no additional steps to the method as defined by claim 7 in order to place the claims in better form for appeal and/or reduce the number of issues on appeal. This amendment does not raise any new issues and does not require further consideration or search. Claim 15, as amended, defines the method of claim 7 to produce changes in the genome of an intact human or animal wherein the single-stranded oligonucleotide is administered into an intact human or animal having a sequence that forms a triple-stranded nucleic acid molecule with the target sequence located in the genome of the intact human or animal, wherein the oligonucleotide binds to the target sequence with a Kd of less than or equal to 2×10^{-7}, and mutates the target sequence. Claim 15

further limits claim 7 because it requires the single-stranded oligonucleotide as defined by claim 7 to be administered to an intact human or animal. One of ordinary skill in the art would clearly understand that the single-stranded oligonucleotide and donor nucleic acid as defined in claim 7 is the same single-stranded oligonucleotide and donor nucleic acid as defined in claims 15-24. Therefore, claims 15-24, as amended, are definite.

Claims 19 and 20 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "DNA fragment." These claims were amended on March 1, 2005 to recite "donor nucleic acid" as recited in the claims from which claims 19 and 20 depend. Claims 19 and 20 are not indefinite because they do not recite "DNA fragment." Furthermore, one of ordinary skill in the art would clearly understand that the donor nucleic acid as defined in claim 7 is the same donor nucleic acid as defined in claims 19 and 20. Claim 19 which depends indirectly from claim 7 defines that the donor nucleic acid **is not** tethered to the single-stranded oligonucleotide. Claim 20 which depends indirectly from claim 7 defines that the donor nucleic acid is tethered to the single-stranded oligunucleotide. Claim 7 does not define whether the donor nucleic acid is tethered or not tethered to the single-stranded oligonucleotide. As clearly described in the specification at least at page 9, lines 11-14, the triplex forming oligonucleotides can be tethered or not to a donor nucleic acid. Therefore, claims 19 and 20 are definite.

Rejection Under 35 U.S.C. § 102

Claims 7-12, 15-21, and 23-25 were rejected under 35 U.S.C. § 102(b) as being anticipated by Chan et al., *Journal of Biological Chemistry* 274:11541-11548 (1999) ("Chan"). Applicants respectfully traverse this rejection.

The present application is a continuation-in-part of U.S.S.N. 09/411,291 filed on October 4, 1999 ("the 1999 application"), which is a divisional of U.S.S.N. 08/476,712 filed on June 7, 1995 ("the 1995 application"), page 1, paragraph 1. The 1999 application, which issued as U.S. Patent No. 6,303,376 ("the '376 patent"), and the 1995 application, which issued as U.S. Patent No. 5,962,426 ("the '426 patent"), provide support under 35 U.S.C. 120 for the claims of the present application. The disclosure of the '376 patent and the '426 patent is the same since the 1999 application which issued as the '376 patent is a divisional of the 1995 application which issued as the '426 patent and contains no new subject matter.

Chan is not prior art as the present application is entitled to a priority date of 1995. Independent claim 7 defines a method for targeted recombination of a nucleic acid molecule (The '376 patent discloses at least at column 3, lines 1-4 that "the binding of the oligonucleotide to the target region stimulates mutations within or adjacent to the target region using cellular DNA synthesis, **recombination**, and repair mechanisms." It is clear from the '376 and '426 patents that the mutations in a region of DNA targeted by a TFO can be accomplished through recombination.) comprising the steps of: a) providing a single-stranded oligonucleotide having a sequence that forms a triple-stranded nucleic acid molecule that form a triple-stranded nucleic acid molecule by hybridizing with a target sequence in a double-stranded nucleic acid molecule

(The '376 patent at least at column 3, lines 58-61 discloses that single-stranded oligonucleotides bind to or hybridize with a predetermined region of a double-stranded DNA molecule so as to form a triple-stranded structure.) with a Kd of less than or equal to 2×10^{-7} (Support can be found in the '376 patent at least at column 5, lines 3-4, and at column 9, lines 25-56, and at Table 1. Table 1 recites that AG20 has a Kd of 3×10^{-7} and AG 30 has a Kd of 2×10^{-8}. These results in Table 1 demonstrate that TFOs with Kd's of 3×10^{-7} or less result in mutagenesis induced by triple helix formation. Since 2×10^{-7} is less than 3×10^{-7}, Kds of less than or equal to 2×10^{-7} are supported by the '376 patent.); and b) providing a donor nucleic acid such that recombination of the donor nucleic acid into the target sequence is induced by triple helix formation between the single-stranded oligonucleotide and the double-stranded nucleic acid molecule (The '376 patent discloses at least at column 3, lines 49-56, that TFOs can be used to stimulate recombination of a DNA fragment into a target region, but does not distinguish between whether the DNA fragment is linked or unlinked. However, at least at that paragraph spanning column 1 to column 2, the '376 patent discloses that TFOs are useful alone or linked to reactive moieties. One of skill in the art would know that the DNA fragment described in the '376 patent at least at column 3, lines 49-56 and at column 6, lines 40-58 could be linked or unlinked to the TFO. This also provides support for dependent claims 9 and 18-20). It is clear that claims 7, 9 and 18-20 are fully supported by the '376 and '426 patents.

Independent claim 15 defines the method of claim 7 to produce changes in the genome of an intact human or animal (The '376 patent describes methods of producing changes in the genome of a human or animal in the specification at least at column 2, lines 11-59. As

mentioned above, the '376 patent discloses at least at column 3, lines 49-56, and again at column 6, lines 40-58, methods in which the TFOs can be used to stimulate homologous recombination of a DNA fragment into a target region.) comprising the steps of: administering the single-stranded oligonucleotide into an intact human or animal (The '376 patent discloses at least at column 5, lines 49-58, that the oligonucleotides are preferably injected into mammals and that it is understood by one or ordinary skill in the art that oligonucleotides are taken up by cells and tissues in animals without special delivery methods.) having a sequence that forms a triple-stranded nucleic acid molecule with the target sequence located in the genome of the intact human or animal, wherein the oligonucleotide binds to the target sequence with a Kd of less than or equal to 2×10^{-7}, and mutates the target sequence. The remainder of the claim language is similar to the language in claim 7 and is supported by the '376 and '426 patents as discussed above. Claim 15 of the present application is fully supported by the disclosures of the '376 and '426 patents.

Dependent claims 8, 12, 16 and 25 are clearly supported by the '376 and '426 patents. As pointed out by the examiner on page 17 of the office action the '376 and '426 patents disclose TFOs of 7 to 40 nucleotides (see column 4, line 4 of the '376 patent) and TFOs of 10, 20, 30 and 57 nucleotides in length. This clearly demonstrates that TFOs of between 10 to 60 nucleotides in length as defined in claim 8 and 16 and at least 30 nucleotides in length as defined in claim 12 is supported by the '376 and '426 patents. Claim 25 defines TFOs between 10 to 40 nucleotides, which is within the range of 7 to 40 nucleotides as defined in the '376 and '426 patents. Therefore, claims 8, 12, 16 and 25 are supported by the '376 and '426 patents.

Support for dependent claims 10 can be found in the '376 patent at least at column 3, lines 47-56 which discloses that a mutation can activate, inactivate or alter the activity and function of a gene containing the target site and that this mechanism can be accomplished when a TFO stimulates homologous recombination of a donor nucleic acid into the target region.

Support for claims 11 and 21 can be found in the '376 patent at least at the paragraph spanning columns 3 and 4 and at column 6, lines 19-31.

Support for claim 17 can be found in the '376 patent at least at column 5, lines 49-50.

Support for claim 22 can be found in the '376 patent at least at column 2, lines 36-38 which discloses that gene therapy is being used on an experimental basis to treat **well known** genetic disorders of humans such as retinoblastoma, cystic fibrosis, and sickle cell anemia. The '376 patent at least at column 6, lines 19-20 discloses that the target gene may contain a mutation that is the cause of a genetic disorder such as a defective cystic fibrosis gene and a defective hemophilia gene or hemoglobin gene as in sickle cell anemia. The examiner notes in the office action on page 18 that the '376 and '426 patents provide support for xeroderma pigmentosum gene. **It was well known to one of ordinary skill in the art that many genes that cause xeroderma pigmentosum (XP) are involved in nucleotide excision repair (NER), especially xeroderma pigmentosum A (XPA), which is discussed in the '376 patent at least at column 7, lines 7-11** (see the enclosed abstract that is a review of XP and the genes that cause XP that are also involved in nucleotide excision repair; Hansson, "Inherited defects in DNA repair and susceptibility to DNA-damaging agents" *Toxicol. Lett.* 64-65 Spec No:141-148 (1992)).

Support for claims 23 and 24 can be found in the '376 patent at least at column 4, lines 7-9.

The claims of the present application are **fully** supported by the '376 and '426 patents. Therefore, Chan is not prior art and claims 7-12, 15-21, and 23-25 are not anticipated by Chan.

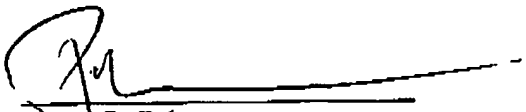
Rejection Under 35 U.S.C. § 103

Claim 22 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Chan. Applicants respectfully traverse this rejection.

As discussed above, the claims of the present application are **fully** supported by the '376 and '426 patents. Therefore, Chan is not prior art as the present application is entitled to a priority date of 1995. Claim 22 is not obvious in view of Chan.

Allowance of claims 7-12 and 15-25 is respectfully solicited.

Respectfully submitted,



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